AMENDMENTS TO THE CLAIMS:

Please replace the claims with the claims provided in the listing below wherein status, amendments, additions and cancellations are indicated.

1. (Currently Amended) A method to predict the topology of the spatial arrangement of an amino acid sequence comprising:

using an entropy evaluation model that takes into account the global contributions of entropy to the folding of a protein ~~biopolymer~~ (herein referred to by the name cross linking entropy (CLE) model ~~and described in the literature~~) combined with other thermodynamic potentials as a protein-folding model to predict said topology.

2. (Currently Amended) A method according to claim 1, wherein using said entropy evaluation model to predict said topology comprises ~~comprising~~ the following steps:

A. inputting an amino acid sequence of [[a]] said protein,

B. preparing information on ~~the~~ secondary structure of ~~the~~ said amino acid sequence by way of at least one theoretical or experimental estimate,

C. applying the CLE model ~~method~~ to ~~the~~ said amino acid sequence and secondary structure information to evaluate the free energy of a combinatorial number of β-strand and α-helix arrangements as rapidly as polynomial time:

$c(n-1)(n+1)$ wherein c is a constant and n is the number of secondary structure elements found in the said amino acid in step A ~~2A~~ and prepared in step B ~~2B~~,

D. applying the CLE model ~~method~~ in conjunction with other thermodynamic

potentials that approximate hydrophobic, electrostatic and polar interactions, but not limited to these aforementioned thermodynamic potentials stated herein, in a thermodynamic calculation to account for both short and long range folding interactions and predict a minimum free energy and corresponding topology of the said amino acid sequence,

E. applying the CLE model ~~method~~ to predict the global folding kinetics of the said amino acid sequence, and

F. storing the information in a data file or in other form of digital memory.

3. (Currently Amended) A method according to claim 1 or 2, in which the cross linking entropy (CLE) model, ~~which is an entropy evaluation model that takes into account the global effects of entropy in the folding of a biopolymer,~~ is used to evaluate the entropy loss of [[a]] said protein due to folding into a particular topology given a known secondary or estimated secondary structure.

4. (Currently Amended) A method according to claim 3, in which an initial theoretical estimate of the secondary structure is obtained from either a theoretical source, or an experimental source. ~~loss of biological activity of the protein can be further predicted.~~

5. (Currently Amended) A method according to claim 4, in which said experimental source is ~~a initial theoretical estimate of the secondary structure is obtained from either a theoretical source, an experimental source such as~~ an NMR experiment or x-ray crystallography, or both.

6. (Currently Amended) A method according to claim 5, in which the theoretical estimate is further supplemented with sequence alignment to find regions in which conserved segments remain ~~remains~~ essentially unchanged by differences in the aligned sequences.

7. (Currently Amended) A method according to claim 5 in which ~~the~~ said amino acid sequence and secondary structure information is used to evaluate the free energy of a combinatorial number of β-strand and α-helix arrangements as rapidly as polynomial time: $c(n-1)(n+1)$, wherein *c* is a constant and *n* is the number of secondary structure elements found in the said amino acid and obtained.

8. (Currently Amended) A method to predict the topology of the spatial arrangement of an amino acid sequence comprising the following steps:

A. inputting an amino acid sequence of a protein,

B. preparing information on ~~the~~ secondary structure of ~~the~~ said amino acid sequence by way of at least one theoretical or experimental estimate,

~~E.~~ C. applying ~~the~~ a CLE model ~~method~~ to approximate the global folding kinetics of the said amino acid sequence,

~~G.~~ D. applying the CLE model ~~method~~ to ~~the~~ said amino acid sequence and secondary structure information to reduce the combinatorial number of β-strand and α-helix arrangements ~~to a computationally manageable number~~, and

~~H.~~ E. applying the CLE model ~~method~~ in conjunction with other thermodynamic potentials that approximate hydrophobic, electrostatic

and polar interactions, but not limited to these aforementioned thermodynamic potentials stated herein, in a thermodynamic calculation to optimize the free energy to find the most thermodynamically favorable topology for ~~the~~ said amino acid sequence,[[-]]

wherein the global free energy (FE) contribution from the CLE between two distinct amino acid residues, herein labeled i and j, is calculated by equation (1):

~~$$\Delta G_{ij} = -T\Delta S_{ij} = \frac{\gamma k_B T}{\xi}\left\{\ln\left(\frac{2\gamma\xi\Delta N_{ij}}{3\lambda_{ij}^2}\right) - 1 + \frac{3\lambda_{ij}^2}{2\gamma\xi\Delta N_{ij}}\right\} \quad (1)$$~~

$$\Delta G_{ij}^{gcle} = -T\Delta S_{ij}^{gcle} = \frac{\gamma k_B T}{\xi}\left\{\ln\left(\frac{2\gamma\xi\Delta N_{ij}}{3\lambda_{ij}^2}\right) - 1 + \frac{3\lambda_{ij}^2}{2\gamma\xi\Delta N_{ij}}\right\} \quad (1)$$

wherein, i and j represent the indices of two distinct residues in ~~the~~ said amino acid sequence, and $j > i$, $\Delta N_{ij} = j - i + 1$ expresses the number of residues separating i and j, ~~ΔG_{ij}~~ ΔG_{ij}^{gcle} is the difference in the free energy contribution to the global CLE from residues i and j transitioning from the denatured (random flight) state to the native state, ~~ΔS_{ij}~~ ΔS_{ij}^{gcle} is the corresponding global entropy loss, ξ is the persistence length, γ is a dimensionless weight parameter describing the self-avoiding properties of a polymer chain, k_B is the Boltzmann constant, T is the temperature, and λ_{ij} (the bond gap) expresses the amino acid separation distance between the center of mass of residue i and the center of mass of residue j when

both are treated as isolated molecules.

9. (Currently Amended) A method according to claim 8, in which the total CLE contribution to the free energy (ΔG_{cle}) is calculated by equation (2):

~~$$\Delta G_{cle} = \Delta G_{\xi}^{o} + \sum_{all\_bonds(i,j)} \Delta G_{ij} + \sum_{i',j'} f_{i'j'}(\xi) \qquad (2)$$~~

$$\Delta G_{cle} = \Delta G_{\xi}^{o} + \sum_{all\_bonds(i,j)} \Delta G_{ij}^{gcle} + \sum_{i',j'} f_{i'j'}(\xi) \qquad (2)$$

wherein, ~~ΔG_{ij}~~ ΔG_{ij}^{gcle} is defined in equation (1), i' and j' are indices specifying two secondary structure elements (α-helices or β-strands) that are joined together by the corresponding set of bonds i and j, $f_{i'j'}(\xi)$ is a positive definite penalty function used to enforce topology constraints on the minimum allowed sequence length of a loop connecting two elements of secondary structure i' j' and is a function of the persistence length ξ, and ΔG_{ξ}^{o} is a renormalization correction and is an integral function of ξ as shown by equation (3):

$$\Delta G_{\xi}^{o} = \frac{(\gamma + 1/2) N k_B T}{D\xi} \int_{+1}^{\xi} \left(\frac{\ln(x)}{(1-x)} + 1 \right) dx \qquad (3)$$

wherein, ξ, γ, k_B, and T mean the same as defined in claim 8 [[7]], N indicates the number of amino acids in the said sequence, D is the dimensionality of the system, the limits in the integral $(1 \rightarrow \xi)$ indicate the change in the number of degrees of freedom from an individual amino acid ~~reside~~ residue to a cluster of ξ amino acids treated as a group (where ξ>1 amino acid and ξ need not be an integer) and x is a dummy variable in the integral substituting for ξ.

10. (Currently Amended) A method according to claim 9, in which ~~the~~ optimal β-sheet alignments are obtained by using thermodynamics.

11. (Currently Amended) A method according to any one of claims 8 to 10, in which the CLE model ~~method~~ is applied in conjunction with other derived or constructed thermodynamic potentials that approximate hydrophobic, electrostatic and polar interactions, in a thermodynamic calculation to account for both short and long range folding interactions and predict a minimum free energy and corresponding topology of ~~the~~ said amino acid sequence.

12. (Withdrawn) A method for building a 3D structure of a protein for MD simulation from the topology obtained by the method according to any one of claims 1,2 and 8-10.

13. (Currently Amended) A method according to claim 1, wherein using said entropy evaluation model to preduct said topology comprises ~~comprising~~ the following steps:

A. obtaining an amino acid sequence of said [[a]] protein,

B. preparing information on ~~the~~ secondary structure of ~~the~~ said amino acid

sequence by way of at least one theoretical or experimental estimate,

~~E.~~ C. applying the CLE model ~~method~~ to approximate the global folding kinetics of the said amino acid sequence,

~~I.~~ D. using the global folding kinetics to predict the optimal topology of the said amino acid sequence, and

~~F.~~ E. storing the information in a data file or in other form of digital memory.